

DIMERIC STATES OF TRANSMEMBRANE SEGMENTS OF THE DDR₁ PREDICTED BY ATOMISTIC MODELING

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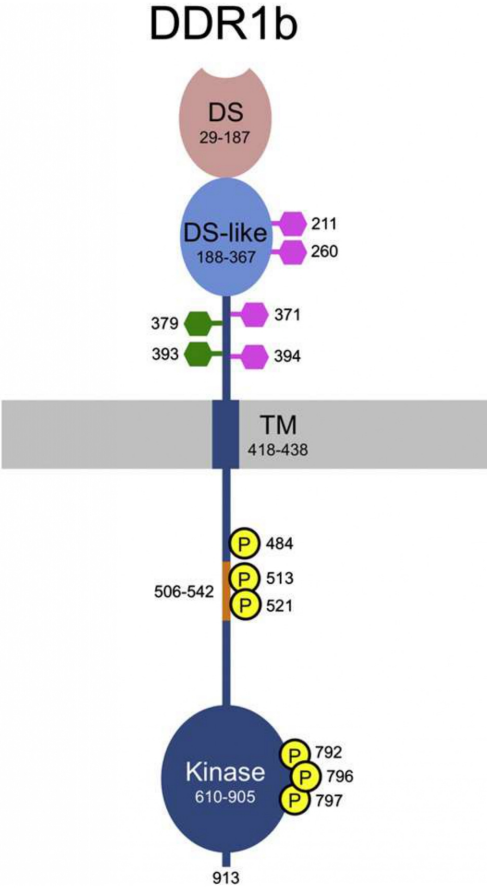
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Russia;*

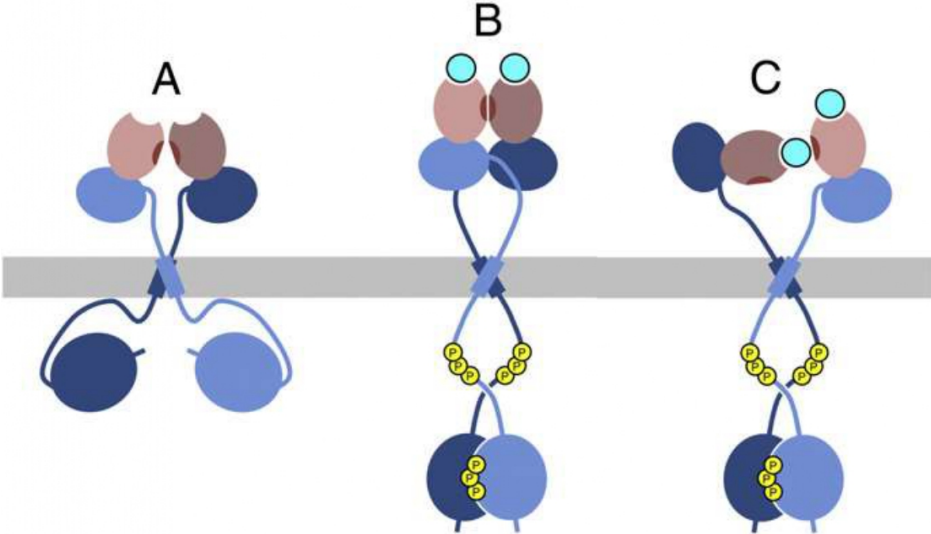
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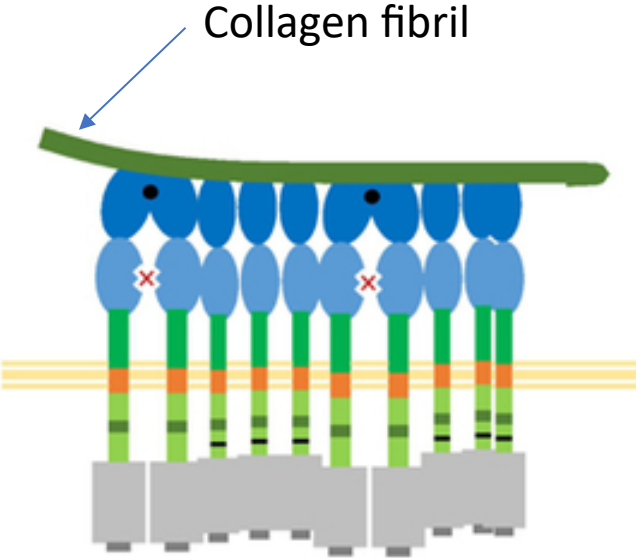
Object of study



DDR1 monomer structure



DDR1 dimers



DDR1 oligomer

Discoidin Domain Receptors: micro insights into macro assemblies, G. Agarwal, A. W. Smith, B. Jones

Goals

Prediction of possible dimeric structures of DDR1 TM domain

- homology modeling
- *de novo* prediction: PredDimer (<https://preddimer.nmr.ru>)
- stability verification of the obtained structures
- stability quantification

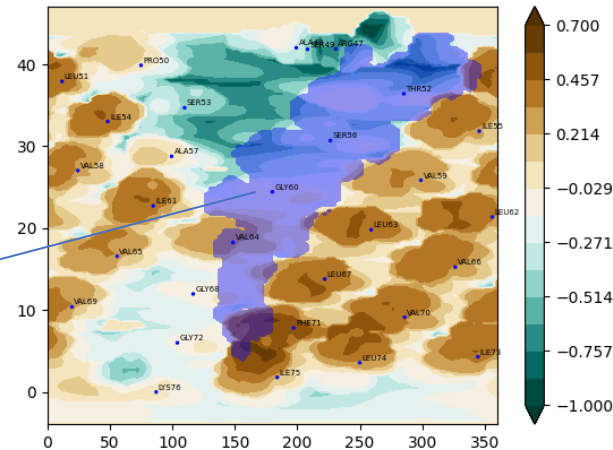
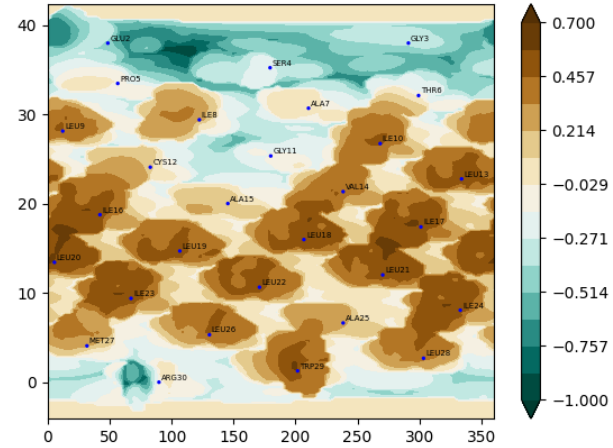
Methods: homology modeling

DDR1 EGSPTAILIGCLVAIILLIILLLIIALML-WR
ERBB2 RASPLTSIISAVVGILLVVVLGVVFGILIK

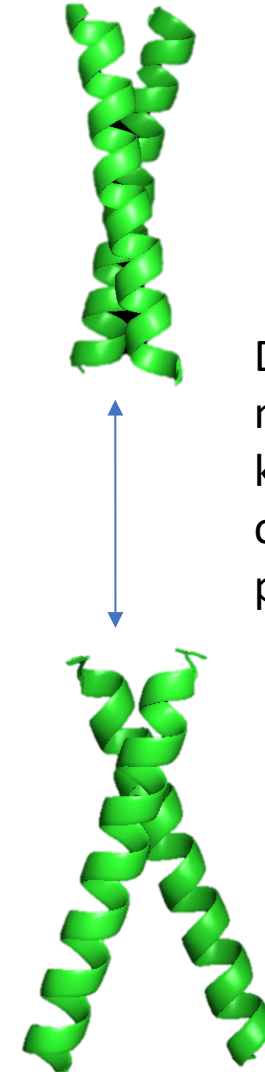
Primary structures comparison

Experimentally defined dimerization interface

MHP — molecular hydrophobicity potential



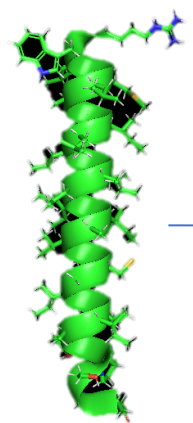
MHP maps comparison



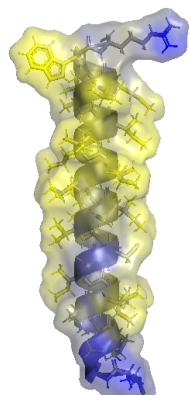
DDR1 dimer model based on known structure of homological protein

Methods: PredDimer

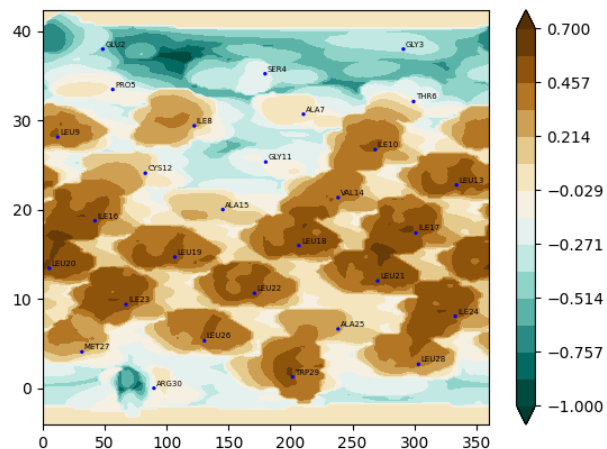
EGSPTAILIGCLVAIIILLLLLLIIALMLWR



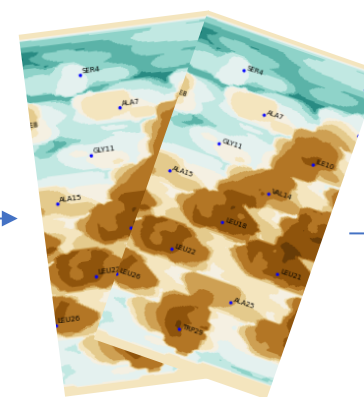
DDR1 monomer



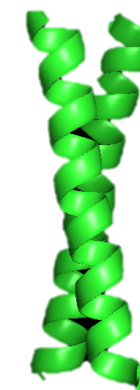
MHP surface



MHP map



MHP maps matching



DDR1 dimer model

MHP — molecular hydrophobicity potential

Prediction results

Homology

2 structures based on ErbB2

DDR1 EGSPTAILIGCLVAIILLLLLIALML-WR

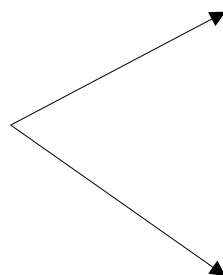
ERBB2 RASPLTSIISAVVGILLVVVIGVVFGLIK

RTK	Identical	Similar	Similar with unitary gaps	Maps MSE
PDGFRB	9	24	14	0.129
ERBB2	7	24	27	0.098
FGFR3	9	20	17	0.122
EPHA2	9	20	21	0.131
EPHA1	6	20	13	0.118
EGFR	7	18	19	0.113
NTRK1	6	18	10	0.142
ERBB3	4	18	11	0.140
ERBB4	3	18	19	0.112

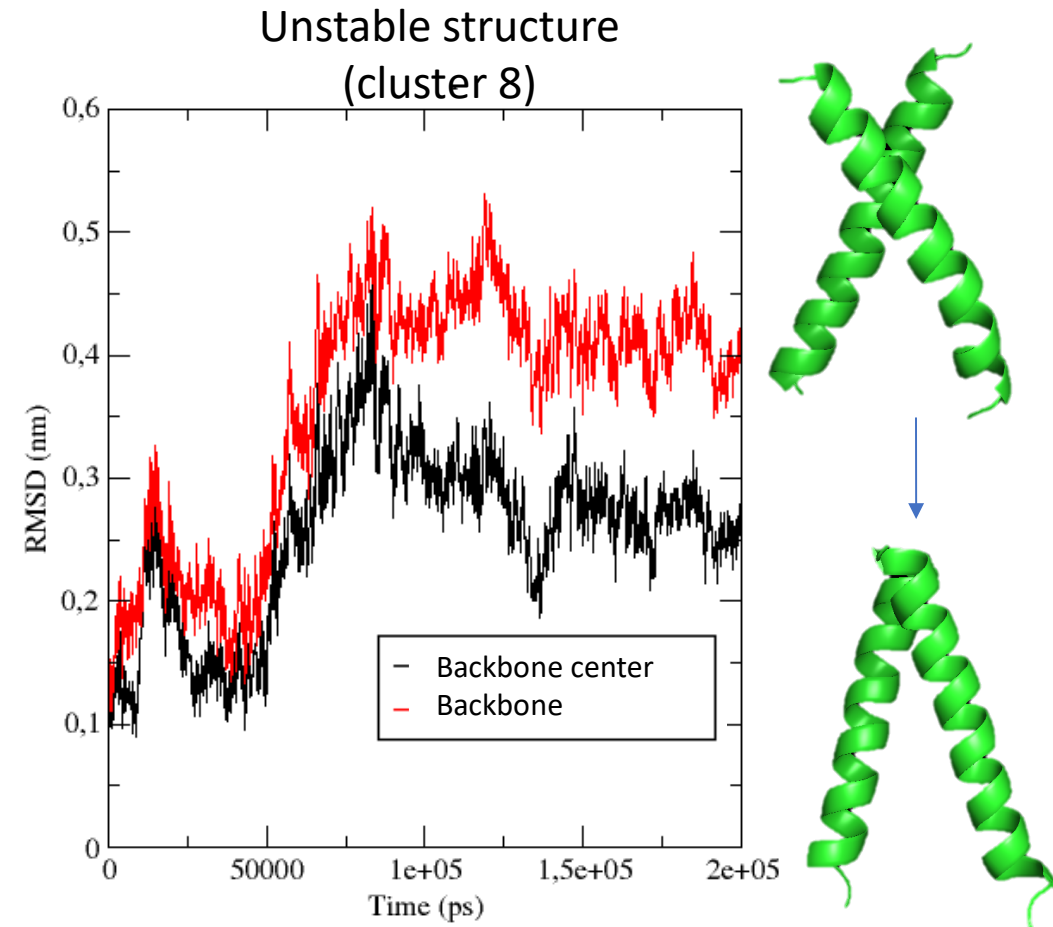
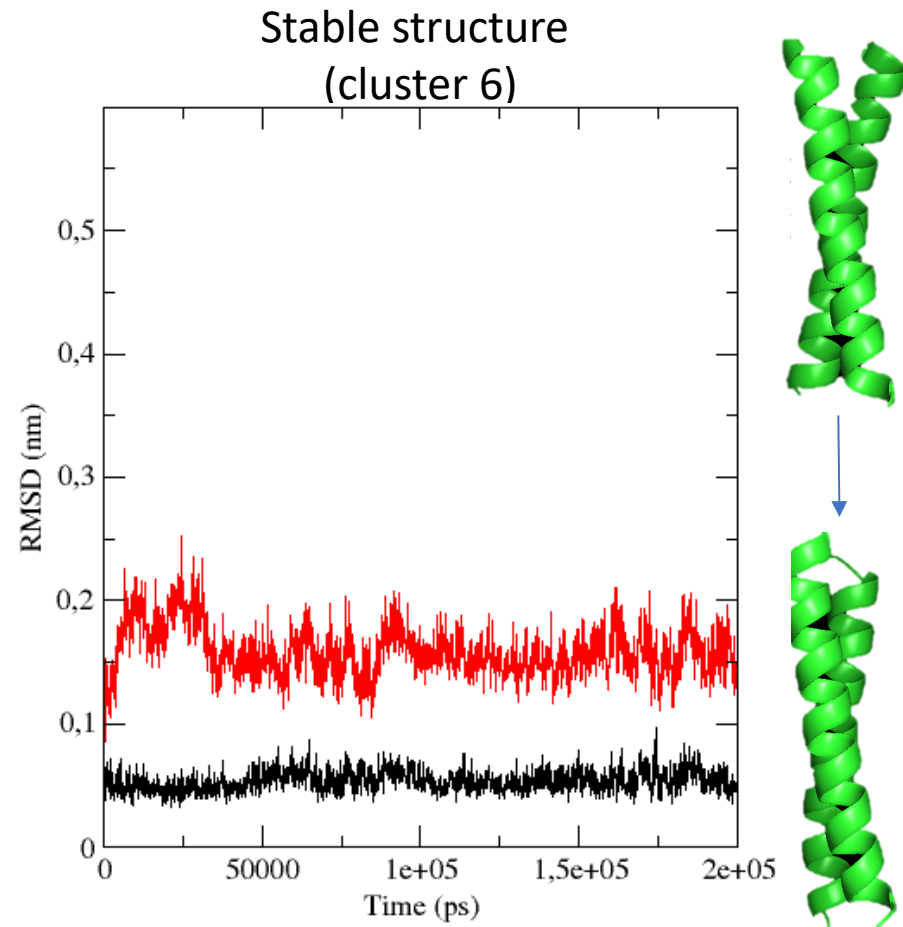
PredDimer

9 clusters of structures

	Dimerization interface	Cross angle	Fscor
	_____G_VA_LL_L_____	-55	2,8
*	_____AI_GC_VA_LL_____	-45	3,3
	_____I_GC_AI_L_I_L_____	-20	2,6
	S_AI_G_VA_L_LL_AL_L	5	3,1
	EG_T_L_L_I_L_I_M	30	1,7
	_G_T_I_L_I_L_I_ML	15	2
*	_____AI_G_V_L_LL_____	35	2,8
	_____I_G_V_L_____	60	2,8
	_____A_L_LL_____LW	40	2,4



Stability verification of obtained structures

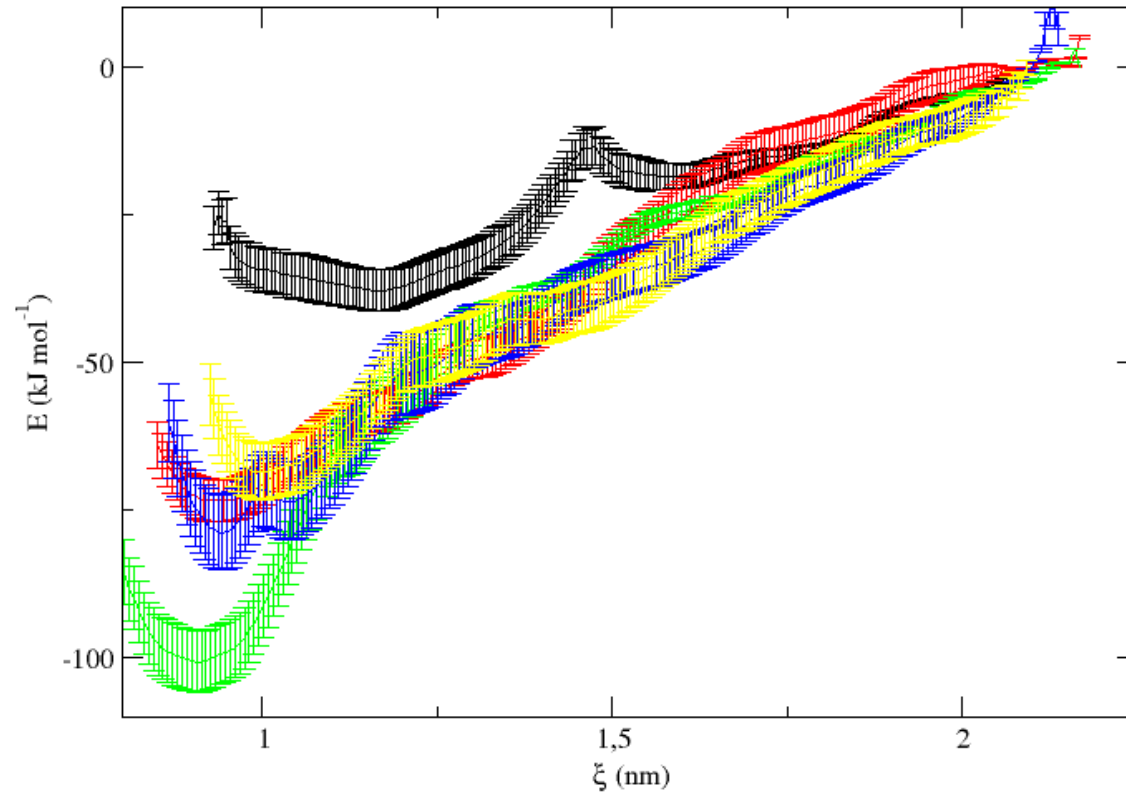


Root-mean-square deviation during molecular dynamics (Gromacs, POPC bilayer, 200ns)

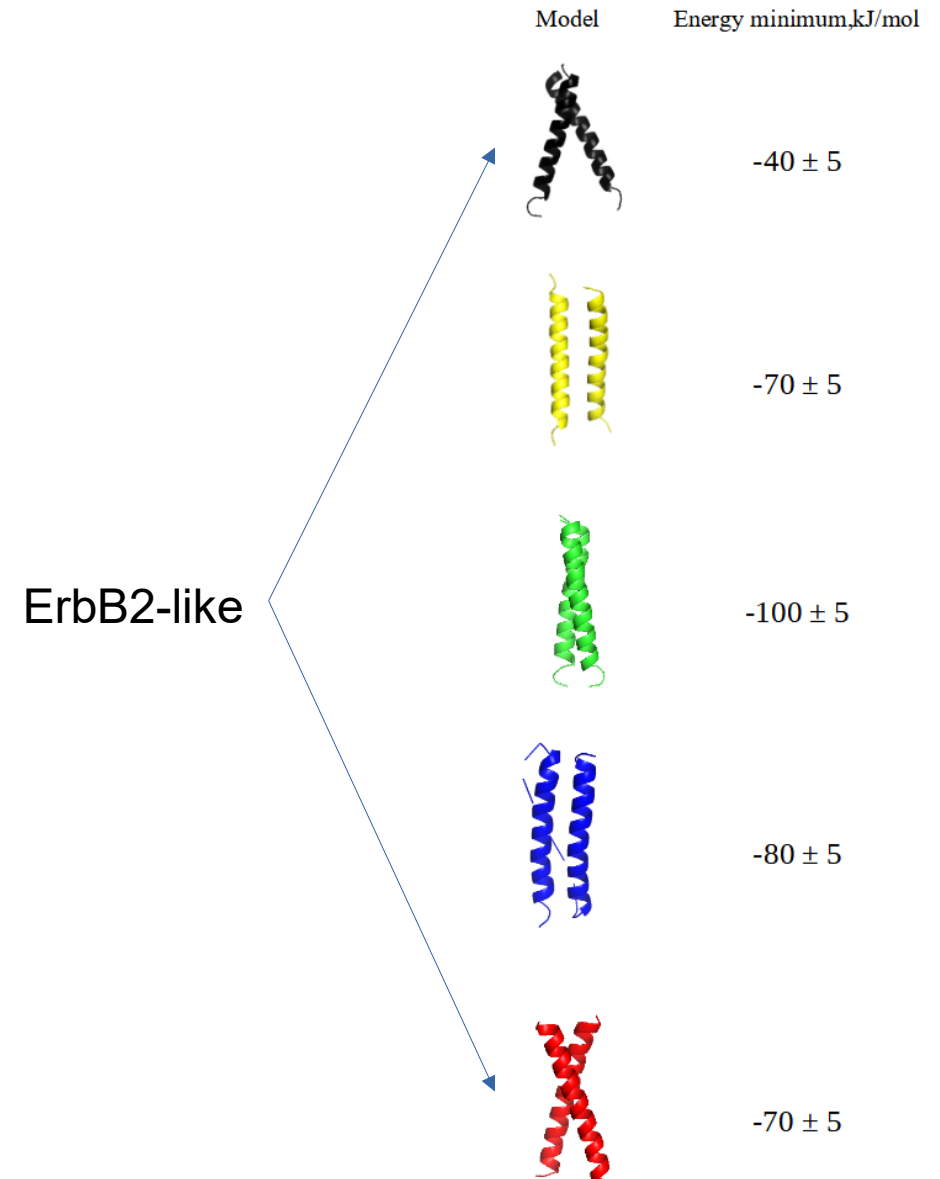
Stability verification of obtained structures

	Dimerization interface	Cross angle	Fscor
	_____G__VA__LL__L_____	-55	2,8
ErbB2-active-like	_____AI__GC__VA__LL_____	-45	3,3
	_____I__GC__AI__L__I__L__	-20	2,6
	S__AI__G__VA__L__LL__AL__L	5	3,1
	EG__T__L__L__I__L__I__M__	30	1,7
	_G__T__I__L__I__L__I__ML	15	2
ErbB2-inactive-like	_____AI__G__V__L__LL_____	35	2,8
	_____I__G__V__L_____	60	2,8
	_____A__L__LL_____LW	40	2,4

Stability quantification



Free energy profiles of stable structures
(USMD, 25-32 windows, 10 ns/window)



Results

- Significant similarity between DDR1 & ErbB2 TMDs → 2 structures by homology
- 9 structures *de novo* (PredDimer)
- 5 models proved to be stable in POPC bilayer, including 2 ErbB2-like
- Quantification of stable structures

Prospects:

- Investigate ErbB2's interceptor peptides influence on DDR1
- Examine ErbB2-DDR1 heterodimerization
- Study polar mutations effects on dimerization

Thank you for your attention